

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ACIBENZOLAR - S- METHYL

Chemical Code # 5338, Tolerance # 52432

4/22/99
Revised: 1/10/06

I. DATA GAP STATUS

Combined, rat:	No data gap; possible adverse effect
Chronic toxicity, dog:	No data gap; No adverse effect
Oncogenicity, mouse:	No data gap; No adverse effect
Reproduction, rat:	No data gap; No adverse effect
Teratology, rat:	No data gap; Possible adverse effect
Teratology, rabbit:	No data gap; No adverse effect
Gene mutation:	No data gap; No adverse effect
Chromosome effects:	No data gap; Possible adverse effect
DNA damage:	No data gap; No adverse effect
Neurotoxicity:	Not required at this time*

Toxicology one-liners are attached.

All record numbers through 215489 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T060110

Moore, 1/10/06

* Rat Subchronic and Developmental Neurotoxicity studies have been submitted. Both studies were unacceptable, but possibly upgradeable.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 061; 162714;** "24-Month Carcinogenicity and Chronic Toxicity Study in Rats"; (H. Frankhauser; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 923151; 2/7/96); Seventy rats/sex/group were fed CGA-245704 Technical (purity: 97.9%) in the diet at concentrations of 0, 20, 200, 2500 or 7500 ppm ((M): 0, 0.77, 7.77, 96.9, 312 mg/kg/day, (F): 0, 0.90, 9.08, 111, 388 mg/kg/day, respectively) for up to 2 years. An additional 10 animals/sex/group were included in an interim sacrifice after 53 weeks of treatment. There was no apparent treatment-related effect on mortality. The mean body weights of the 7500 ppm group were lower over the course of the study ($p < 0.01$). The mean water consumption level for these animals was increased ($p < 0.01$). The percentage increase of the reticulocyte levels in the erythrocyte count was significant for the 7500 ppm group at various times during the study ($p < 0.01$). This observation was noted in conjunction with the increased incidence and severity of hemosiderosis in the spleens of the 2500 and 7500 ppm treatment groups as well as the increased incidence of this lesion in the liver Kupffer cell of the 7500 ppm group and the increased mean spleen weights for the 7500 ppm group. There were other apparent treatment-related effects of increased total bilirubin levels and reduced globulin levels in the serum of the high dose group ($p < 0.1$) and the increased incidence and severity of foam cells in the lung alveoli of the high dose females. The mucinous carcinoma was noted among the male rats in the 200, 2500 and 7500 ppm treatment groups with an incidence of 1/60, 1/59 and 2/59. This level of incidence was well in excess of that for the historical control (one case in 12 studies evaluated). **Adverse effect:** incidence of mucinous carcinoma in the small intestine. **Chronic NOEL (M/F):** 200 ppm (M: 7.77 mg/kg/day, F: 9.08 mg/kg/day) (based upon the increased incidence of splenic hemosiderosis in the 2500 ppm treatment group); **Study acceptable.** (Moore, 3/15/99)

CHRONIC TOXICITY, DOG

**** 052; 162705;** "12-Month Chronic Oral Toxicity Study in Beagle Dogs"; (B. Altmann; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Test No. 923149; 1/30/96); Four dogs/sex/group were dosed with 0, 5, 25 or 200 mg/kg/day of CGA-245704 Technical (purity: 97.9%) for 52 weeks. The test material was administered in gelatin capsules. One male was euthanized on day 183 after displaying excessive moribundity. Gross examination revealed a pulmonary infection. The animals in the 200 mg/kg/day group exhibited reduced body weight gain during the first 6 months of the study, recovering to the level of the control group by the end of the study. The mean rbc count was reduced in the high dose males ($p < 0.01$) throughout the study. Likewise, the 5 and 25 mg/kg group animals had reduced counts on week 26 ($p < 0.05$ and 0.01 , respectively) and the 25 mg/kg group on week 52 ($p < 0.01$). The mean counts for the high dose females were reduced on weeks 13 and 52 ($p < 0.05$). The mean hemoglobin concentrations were likewise reduced in the same groups at the same time points as well as the 5 mg/kg group at 52 weeks ($p < 0.05$). The mean hematocrit levels were similarly reduced with the most severe effect on the high dose males. The percentage of basophils in the differential wbc count was reduced in the high dose males (weeks 13 ($p < 0.01$), 26 ($p < 0.05$) and 52 ($p < 0.05$)) and females (weeks 13 ($p < 0.01$) and 26 ($p < 0.05$)). Mean urea levels were increased in the high dose animals with a significant level achieved in the females at 52 weeks ($p < 0.05$). Triglyceride levels were significantly increased in the 200 mg/kg group (males, week 13 ($p < 0.05$), 26 ($p < 0.05$), 52 ($p < 0.01$), females, week 26 ($p < 0.05$)) and the 25 mg/kg males (week 52 ($p < 0.05$)). The mean cholesterol levels were increased in the high dose group with significance achieved in the females on week 13 ($p < 0.05$). Likewise, the mean total bilirubin level was increased in both the high dose males and females and in the 25 mg/kg females by week 52 ($p < 0.05$). Mean serum calcium levels were reduced in the high dose males on weeks 13, 26, and

52 ($p < 0.01$). Although the serum alkaline phosphatase levels were increased in the high dose females (week 13 and 26 ($p < 0.05$)), the increases were not sufficiently elevated to indicate frank tissue injury. Mean liver weight was greatest in the high dose females ($p < 0.05$). The mean spleen weight was least in the high dose males ($p < 0.05$). Liver histopathology included an increased incidence of hemosiderosis of Kupffer cells (control, M and F: 0/4; 200 mg/kg, M and F: 3/4), intrahepatic cholestasis (control, M and F: 0/4; 200 mg/kg, M and F: 3/4) and inflammatory cell infiltration (control, M and F: 0/4; 25 mg/kg, M: 0/4, F: 1/4; 200 mg/kg, M: 2/4, F: 3/4). In the spleen, increased incidences of extramedullary hematopoiesis (control, M and F: 0/4; 200 mg/kg, M: 1/4, F: 4/4) and hemosiderosis (control: M: 2/4, F: 1/4; 5 mg/kg: M: 1/4, F: 2/4; 200 mg/kg: M: 3/4, F: 4/4) were noted. **No adverse effects indicated. NOEL (M):** 5 mg/kg/day (based upon treatment-related effects on the rbc counts and the hemoglobin concentration in the 25 mg/kg/day group; **NOEL (F):** 25 mg/kg/day (based upon the lesions noted in the liver and spleen of the 200 mg/kg/day treatment group). **Study acceptable.** (Moore, 1/20/99)

ONCOGENICITY, MOUSE

** 053; 162706; "CGA-245704 Technical: 18-Month Oncogenicity Study in Mice"; (H. Frankhauser; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Test No. 923150; 1/31/96); Fifty mice/sex/group were treated in the diet with 0, 10, 100, 2000 or 6000 ppm of CGA-245704 Technical (purity: 97.9%) for 18 months ((M): 0, 1.14, 11.1, 237, 698 mg/kg/day, (F): 0, 1.14, 10.8, 234, 696 mg/kg/day, respectively). An additional 10 animals/sex/group were treated for the duration of the study and used for the hematological evaluation. There was no treatment-related effect on survival. The mean body weights of the high dose animals were lower than those of the control animals at various times during the study ($p < 0.01$). There was a treatment-related effect upon the red blood cells. The mean rbc count and hematocrit were reduced for the females in the high dose group ($p < 0.01$) at both 53 and 79 weeks. The reticulocyte fraction for these females was increased ($p < 0.01$). In addition, a dose-related increase in hemosiderosis of the spleen, bone marrow and liver was noted for both males and females. The mean spleen weight was increased for the high dose females ($p < 0.01$) and reduced for the high dose males ($p < 0.01$). Other non-neoplastic lesions which demonstrated a treatment-related incidence were foam cells in the lung of the 6000 ppm treatment group and hyperplasia of the exocrine pancreas in the males of the high dose group. For neoplasms, in the harderian gland, there was an increased incidence of carcinomas and adenomas for the males in the 2000 ppm group (15/50 versus the control incidence of 6/50) and adenomas for the males in the 100 (12/50) and 6000 ppm groups (12/50). However, the incidence of these lesions was within the historical control values and was not considered to be toxicologically significant. In addition, a similar effect was not noted for the females. **No adverse effect indicated. Chronic NOEL: (M/F)** 100 ppm (M: 11.1 mg/kg/day, F: 10.8 mg/kg/day) (based upon the increased incidence of hemosiderosis in the bone marrow and spleen of the 2000 ppm treatment group) ; **Study acceptable.** (Moore, 2/5/99)

REPRODUCTION, RAT

** 059; 162712; "CGA-245704 Technical: Two-Generation Reproduction Study in Rats"; (S. Khalil; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 923152; 12/4/95); Thirty rats/sex/group were dosed orally in the diet with 0, 20, 200, 2000 or 4000 ppm of CGA-245704 Technical (purity: 97.9%) for two generations (F0 and F1). The treatment periods included 10 weeks prior to mating, 3 weeks gestation and 3 weeks lactation. At that time, 30 F1a animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation. At the time the F1a offspring were weaned, the F0 parents were remated and produced F1b offspring with treatment continuing through gestation and lactation. No treatment-related mortality resulted from the treatment. The mean body weights for the F1 adults in the 4000 ppm treatment group were lower than those of the control animals ($p < 0.01$). Histological examination revealed an increased incidence and severity

of splenic hemosiderosis in the F0 and F1 males and females at 2000 and 4000 ppm. There were no effects upon any of the parameters of reproduction. The mean pup weights in the 2000 and 4000 ppm groups were lower by 21 days of lactation than those of the controls ($p < 0.01$). **No adverse effect indicated. Parental NOEL:** 200 ppm (based upon the increased incidence and severity of splenic hemosiderosis in the 2000 ppm treatment group) ((M) 8.8 to 30.7 mg/kg/day, (F) 11.6 to 43.6 mg/kg/day); **Reproductive NOEL:** 4000 ppm (HTD) ((M) 171.3 to 604.0 mg/kg/day, (F) 234.6 to 792.0 mg/kg/day); **Developmental NOEL:** 200 ppm (based upon lower mean pup weight for the F1 and F2 offspring) ((M) 8.8 to 30.7 mg/kg/day, (F) 11.6 to 43.6 mg/kg/day); **Study acceptable.** (Moore, 3/10/99)

113; 165585; "CGA-245704 Technical: Rangefinding Rat Dietary Reproduction Study"; (J.H. Marty; Short-/Long-term Toxicology, Novartis Crop Protection, Inc., (Formerly Ciba-Geigy Limited), 4332 Stein, Switzerland; Report No. 923146; 10/29/93); Fifteen rats/sex/group were treated in the diet with 0, 2000, 4000 or 8000 ppm of CGA-245704 Technical (purity:97.9%) (approximately 0, 200, 400 and 700 mg/kg/day, respectively). Mating was initiated two weeks after the beginning of dosing. The study was terminated at the end of the weaning period except for 5 litters/dose group which were maintained for an additional 3 weeks. No mortality resulted the treatment. The mean body weights of both the males and females in the 8000 ppm groups and of the females during the lactation period in the 4000 ppm group were lower than the control values ($p < 0.01$). Five of the dams in the 8000 ppm group dams suffered vaginal bleeding. There was no effect upon mating or the fertility parameters (nos. of corpora lutea and implanation sites/animal). None of the dams in the 8000 ppm group delivered. Otherwise, there were no effects on reproduction noted at the lower dosing levels. The development of the pups in the 4000 ppm group was affected with lower mean body weights from day 7 through day 42 postnatal. **Possible adverse effect:** total loss of fetuses; **Maternal NOEL:** 4000 ppm (400 mg/kg/day) (based on lower mean body weights for the animals in the 8000 ppm group); **Reproduction NOEL:** 4000 ppm (400 mg/kg/day) (based upon the loss of offspring in the 8000 ppm treatment group), **Developmental NOEL:** 2000 ppm (200 mg/kg/day) (based on the lower mean body weights of the pups in the 4000 ppm treatment group). **Supplemental Study.** (Moore, 3/24/99)

TERATOLOGY, RAT

**** 054; 162707;** "CGA-245704 Technical: Rat Oral Teratogenicity"; (J.H. Marty; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 923139; 3/21/94); Twenty four mated females/group were treated by oral gavage with 0, 10, 50, 200 or 400 mg/kg/day of CGA-245704 Technical (purity: 97.9%) from day 6 through day 15 of post-coitum. No mortality resulted from the treatment. The high dose dams demonstrated reduced mean body weight gain and hemorrhagic discharge in the perineal area. Treatment-related effects upon fetal development included increased early resorption and fetal malformations in the 400 mg/kg/day treatment group. Eighty seven percent of the prospective fetuses suffered early resorption. In addition, 26% of the surviving fetuses exhibited malformations. Treatment-related developmental effects on the fetuses in the 200 mg/kg/day group were limited to the absence of ossification in various bones ($p < 0.01$). **Possible adverse effects:** increased incidence of treatment-related implantation loss and fetal malformations; **Maternal NOEL:** 200 mg/kg/day (based upon reduced body weight gain and hemorrhagic discharge in the perineal area noted for the dams in the 400 mg/kg/day group); **Developmental NOEL:** 50 mg/kg/day (based upon absent ossification of the proximal phalanges and other bones in the fetuses of the 200 mg/kg/day group); **Study acceptable.** (Moore, 2/22/99)

**** 058; 162711;** "CGA-245704 Technical: Rat Dermal Teratogenicity"; (S. Khalil; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 943001; 8/22/94); Twenty four mated females/group were treated dermally for 6 hours/day with 0,

10, 100, or 500 mg/kg/day of CGA-245704 Technical (purity: 97.9%) from day 6 through day 15 of post-coitum. No mortality resulted from the treatment. No treatment-related effects were noted. There were no treatment-related effects upon fetal development. **No adverse effects indicated. Maternal NOEL:** 500 mg/kg/day (HTD), **Developmental NOEL:** 500 mg/kg/day (HTD); **Study acceptable.** (Moore, 3/1/99)

Range-finding Teratology Studies

056; 162709; "CGA-245704 Technical: Range Finding Rat Oral Teratogenicity (Non Standard Study)"; (S. Khalil; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 943067; 7/1/94); Twelve mated females/group were dosed orally by gavage with either 0 or 300 mg/kg/day of CGA-245704 Technical (purity: 97.9%). Group 1 was treated with the vehicle. Group 2 was treated with the test material from day 6 to day 15 of gestation. Groups 3 through 7 were treated with the test material on days 6-7, 8-9, 10-11, 12-13, and 14-15, respectively. No mortality resulted from the treatment. The treated females exhibited a bloody vaginal discharge with Group 2 having the highest number per group. An increased incidence of early resorptions was also noted for Group 2. Although Groups 4 and 6 also exhibited an increase in the number of early resorptions, continued dosing throughout the 10 day period was an apparent factor for increasing the overall incidence of resorption. **Possible adverse effect indicated:** increased incidence of early resorption. **Maternal NOEL**<300 mg/kg/day (based upon the presence of vaginal hemorrhage for the females in the 300 mg/kg/day treatment group); **Developmental NOEL**< 300 mg/kg/day (based upon the increased incidence of early resorption and reduced fetal weight for the fetuses in the 300 mg/kg/day treatment group); **Supplemental Study.** (Moore, 2/24/99)

057; 162710; "CGA-245704 Technical: Range Finding Rat Oral Teratogenicity (Non Standard Study)"; (S. Khalil; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 943004; 7/18/94); Eight mated females/group were dosed orally by gavage with either 0 or 400 mg/kg/day of CGA-245704 Technical (purity: 97.9%). Group 1 was treated with the vehicle from day 6 to day 15 of gestation. Group 2 through 6 were treated with the test material on days 6-7, 8-9, 10-11, 12-13, and 14-15, respectively, of gestation. One female in Group 2 was found dead on day 20. One female in Group 2 and 4 females in Group 3 had hemorrhagic perineal discharge with all of the animals in the latter group suffering total resorption of their fetuses. The greatest treatment-related effects were noted for the females in Group 3 indicating that treatment on days 8 and 9 resulted in the greatest risk for early resorption of the fetuses. **Possible adverse effect:** early fetal resorption. **Maternal NOEL** <400 ppm (based upon the incidence of bloody vaginal discharge for the treated animals); **Developmental NOEL** < 400 ppm (based upon the increased incidence of early resorption in the treated Group 3). **Study supplemental.** (Moore, 3/1/99)

TERATOLOGY, RABBIT

**** 055; 162708;** "CGA-245704 Technical: Rabbit Oral Teratogenicity"; (J.H. Marty; CIBA-GEIGY Limited, Short-/Long-term Toxicology, 4332 Stein, Switzerland; Study No. 923140; 4/18/94); Seventeen artificially-inseminated female rabbits/group were dosed orally by gavage with 0, 10, 50, 300 or 600 mg/kg/day of CGA-245704 Technical (purity: 97.9%) from day 7 to day 19 of gestation. Six of the females in the 600 mg/kg/day group died (three were found dead on days 13, 22 and 25 and 3 were euthanized in moribund condition, 2 on day 24 and one on day 28). One female in the 300 mg/kg/day treatment group died on day 18. Three of the high dose decedents and the one in the 300 mg/kg group exhibited hemorrhage of the stomach in the postmortem exam. Otherwise, there were no treatment-related effects noted for the surviving animals. There were no treatment-related effects upon the development of the fetuses. **Maternal NOEL:** 50 mg/kg/day (based upon the mortality of doe in the 300 mg/kg/day), **Developmental NOEL:** 600 mg/kg/day (HTD); **Study acceptable.** (Moore, 2/23/99)

GENE MUTATION

** 064; 162717; "Gene Mutation Test with Chinese Hamster Cells V79 *In Vitro*"; (D. Geleick, Genetic Toxicology, Ciba-Geigy Limited, Basle, Switzerland; Test No. 923141; 11/17/93); Chinese hamster V79 cells were exposed to CGA-245704 Technical (purity: 97.9%) at concentrations ranging from 37.04 to 1000.0 µg/ml (activated) or 3.70 to 100.00 µg/ml (non-activated) for 5 hours (activated) or 21 hours (non-activated) at 37° C. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related effect upon the forward mutation frequency. **No potential adverse effect evident. Study acceptable.** (Moore, 3/16/99)

** 065; 162718; "CGA-245704 Technical: *Salmonella* and *Escherichia*/Liver Microsome Test, Gene Mutation Test"; (Th. Hertner; Genetic Toxicology, Ciba-Geigy Limited, Basle, Switzerland; Test No. 923145; 8/23/93); *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-245704 Technical (purity: 97.9%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation in two trials. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study acceptable.** (Moore, 3/18/99)

CHROMOSOME EFFECTS

** 062; 162715; "CGA-245704 Technical: Micronucleus Test Mouse (OECD Conform) *In Vivo* Study"; (Th. Hertner; Genetic Toxicology, Ciba-Geigy Limited, Basle, Switzerland; Test Number 923143; 10/27/93); Five mice/sex/group were dosed orally by gavage with 0, 1000, 2000 or 4000 mg/kg of CGA-245704 Technical (purity: 97.9%) or the positive control, cyclophosphamide (64 mg/kg), and euthanized 24 hours after dosing. Additionally, 5 animals/sex/group/time point were treated with 0 or 4000 mg/kg of the test material and euthanized at 16 or 48 hours after dosing. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). One thousand PCEs were evaluated per animal. The ratio of PCEs to normocytic erythrocytes was noted as well. There was no treatment-related increase in the number of PCE with micronuclei per 1000 PCEs. **No adverse effect indicated. Study acceptable.** (Moore, 3/17/99)

** 063; 162716; "CGA-245704 Technical: Cytogenetic Test in Chinese Hamster Cells *In Vitro* (EC-Conform)"; (Th. Hertner; Genetic Toxicology, Ciba-Geigy Limited, Basle, Switzerland; Test No. 923142; 10/18/93); Chinese hamster ovary (CCL61) cells were exposed to CGA-245704 Technical (purity: 97.9%) at concentrations ranging from 0 to 30 µg/ml with and w/o activation (trial #1) or 0 to 60 µg/ml with and w/o activation (trials #2 and 3). In trials 1 and 2, the cells were exposed to the test material for 18 hours w/o activation or 3 hours with activation, followed by a 15 hour recovery period. In trial #3, cells were treated for 42 hours w/o activation or 3 hours with activation, followed by a 39 hour recovery period. Incubations were performed at 37° C with duplicate cultures/treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. An increase in the percentage of cells with chromosomal aberrations was noted in the non-activated assays (trials #2 and 3) for the treatment levels of 30 (p<0.05) and 60 µg/ml (p<0.001) after 18 hours of incubation and for the treatment levels of 15 (p<0.05), 30 and 60 µg/ml (p<0.01) after 42 hours of incubation. No treatment-related effects were evident in the activated samples. **Potential adverse effect:** increased percentage of cells with chromosomal aberrations under conditions of non-activation. **Study acceptable.** (Moore, 3/17/99)

DNA DAMAGE

** 069; 162722; "CGA-245704 Technical: Autoradiographic DNA Repair Test on Rat Hepatocytes (OECD Conform) *In Vitro*"; (Th. Hertner; Genetic Toxicology, Ciba-Geigy

Limited, Basle, Switzerland; Test No. 923144; 8/23/93); Primary rat hepatocyte cultures were exposed to CGA-245704 Technical (purity: 97.9%) at concentrations ranging from 9.77 to 312.5 µg/ml (trial #1) or 15.63 to 500 µg/ml (trial #2) for 16 to 18 hours at 37° C. Vehicle control (DMSO: 1%) and positive control (2-acetylaminofluorene: 45 µM) cultures were included in the assay. There were 3 cultures per treatment level in the two trials. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated. Study acceptable.** (Moore, 3/18/99)

NEUROTOXICITY

52432-0154; 215489; "90-Day Subchronic Neurotoxicity Study in Rats"; (W. Classen; Toxicology/Experimental Toxicology, Novartis Crop Protection AG, 4332 Stein, Switzerland; Study No. 963028; 8/19/97); Ten Tif: RAlf rats/sex/group received 0, 400, 2000, or 8000 ppm of CGA 245704 technical (batch no. P. 303011, purity: 97.9%) in the diet for 13 weeks ((M) 0, 24.4, 125.9, 575.2 mg/kg/day, (F) 0, 26.0, 142.5, 627.9 mg/kg/day). No treatment-related clinical signs were evident through out the study. The mean body weights and food consumption of both sexes in the 8000 ppm treatment group were lower than that of the control group during the study (p<0.01). There were no apparent treatment-related effects evident in the Functional Observational Battery or motor activity assessment. No treatment-related neurological lesions were noted in the histopathological evaluation. **No adverse effect evident. Reported Subchronic Neurotoxicity NOEL: 8000 ppm ((M) 575.2 mg/kg/day, (F) 627.9 mg/kg/day)** (based upon the lack of a treatment-related neurological effect on the highest treatment level); **Study unacceptable**, possibly upgradeable with the submission of positive control data). (Moore, 8/16/05)

52432-0153; 215488; "CGA-245704 Technical (Acibenzolar-S-Methyl): Developmental Neurotoxicity Study in Rats"; (P.J. Pinto; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. RR0930; 11/12/02); Thirty time-mated female Alp:AP_iSD (Wistar-derived) rats/group received 0, 100, 1000 or 4000 ppm of CGA-245704 Technical (batch no. P.303011, purity: 97.9%) in the diet from day 7 of gestation through day 22 of *post-partum* (gestation: 0, 8.2, 82, 326.2 mg/kg/day, lactation: 0, 15.5, 153.6, 607.8 mg/kg/day). The F1 offspring were culled on day 5 *post partum*. At least 10 pups/sex/group were examined in the Functional Observational Battery on days 5, 12, 22, 36, 46 and 60 *post partum*. One pup/sex/litter/group was examined for motor activity on days 14, 18, 22 and 60 *post partum*. One pup/sex/litter/group was examined in the auditory startle response assessment on days 23 and 61 *post partum*. One pup/sex/litter/group was assigned to the learning and memory test. The learning phase was performed on days 21 and 59 *post partum*. The memory test was performed on days 24 and 62. On day 12 *post partum*, one pup/sex/litter/group was euthanized. The brain weights were recorded and the brain examined histologically. On day 63 *post partum*, one animal/sex/litter/group was euthanized and the brain weights were recorded. An additional 10 animals/sex/group were euthanized by perfusion fixation The brain weights were recorded as well. The appropriate neuronal and muscle tissues were examined histologically. The brains from both the 12 day old pups and the 63 day old young adults were assessed morphometrically. There was no treatment-related effect noted on the mean body weights or the food consumption of the dams. The reproductive performance of the dams was not affected. There was no apparent treatment-related effect in the time to maximum amplitude in the auditory startle test. In the auditory startle test, the 4000 ppm F1 females demonstrated an increased startle amplitude at 23 days (p<0.05 or 0.01). This effect was not evident at the 61 day assessment. In the learning and memory assessment, the 4000 ppm F1 females had a lower percentage of the test animals successfully completing the test at the respective cut off times than the control group at 59 days *post partum* (NS or p<0.05). There was no indication of an effect for the F1 males. At 62 days, in the memory phase, no treatment-related effect was evident. In the brain morphometry, the thickness of the dorsal cortex was less for all of the F1 male treatment groups in comparison with the control at 63 days (p<0.05 or 0.01). However, there was no apparent dose-response. The thickness of preculminate and prepyramidal fissures was less for all of the F1 male treatment groups at 63 days as well in comparison to the control (NS, p<0.05 or 0.01). There was no apparent treatment-related effect on brain morphometry of the F1 females. **No adverse effect indicated. Reported Developmental Neurotoxic NOEL: 4000 ppm (326.2 mg/kg/day)** (based

up the lack of a treatment-related effect at the highest treatment level). **Study unacceptable**, possibly upgradeable with the submission of positive control data). (Moore, 8/18/05)

STUDIES ON METABOLITES

066; 162719; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Toxicology, Genetic Toxicology, Novartis Crop Protection, AG, CH-4002 Basel, Switzerland; Test No. 973097; 2/20/98); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with NOA-419191 (by-product of CGA-245704 Technical) (purity: 98%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation in two trials. In the second trial with activation, the test material was preincubated for 30 minutes at 37° C with the test material prior to plating. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study supplemental** (test material was a byproduct of the subject product under consideration). (Moore, 3/19/99)

067; 162720; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (E. Deparade; Toxicology, Genetic Toxicology, Novartis Crop Protection, AG, CH-4002 Basle, Switzerland; Test No. 973079; 1/26/98); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-362020 Technical (isomer of CGA-245704 Technical) at concentrations ranging from 61.73 to 5000 µg/plate with activation and 30.86 to 2500 µg/plate w/o activation in two trials. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Treatment of the TA 1537 strain without activation resulted in an increase in the number of revertant colonies, a possible frame shift mutation. **Possible adverse effect indicated. Study supplemental** (test material is an isomer of the subject product under consideration). (Moore, 3/19/99)

068; 162721; "*Salmonella* and *Escherichia*/Mammalian-Microsome Mutagenicity Test"; (B. Ogorek; Toxicology, Genetic Toxicology, Novartis Crop Protection, AG, CH-4002 Basle, Switzerland; Test No. 963125; 1/30/97); *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1357, *E. coli* strain WP2 uvrA were treated for 48 hours at 37° C with CGA-323060 Technical (plant metabolite of CGA-245704 Technical) (purity: 98%) at concentrations ranging from 312.5 to 5000 µg/plate with and w/o activation in two trials. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. The second trial with activation was performed using a 30 minute preincubation period at 37° C with the test material prior to plating. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study supplemental** (test material was a plant metabolite of the subject product under consideration). (Moore, 3/19/99)

SUBCHRONIC STUDIES

(90 Day Feeding Studies)

048; 162700; "3-Month Oral Toxicity Study in Rats (Administration in Food)" (Bachmann, M., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Test No. 923082, 8/20/93). 821. CGA 245704 tech. (Batch No. KGL 4208, purity=90.9%) was admixed to the pelleted food at concentrations of 0, 40, 400, 2000, or 8000 ppm (0, 2.42, 24.6, 126, or 516 mg/kg/day, respectively, for males and 0, 2.64, 26.3, 131, or 554 mg/kg/day, respectively, for females) and fed to 10 Tif: RAIf (SPF) hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level [with 10 additional rats per sex per dose level at the 0 and 8000 ppm levels to test recovery (4 week recovery period used)] continuously for a period of 3 months. No animals died. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weights was observed in both males and females at 8000 ppm during treatment (recovery group animals indicate reversibility of this effect). A treatment-related increase in mean white blood cell count in both males and females and a treatment-related decrease in mean hemoglobin in males only were observed at 8000 ppm at Week 14 (recovery group animals indicate

reversibility of these effects). A treatment-related increase in mean creatinine levels was observed in both males and females at 8000 ppm at Week 14 (recovery group animals indicate reversibility of this effect). Treatment-related increases in mean relative liver, spleen, and kidney weights in both males and females at 8000 at Week 14 were observed (partial but not complete reversibility indicated). Microscopic examination revealed glycogen deposition in the hepatocytes (reversibility indicated) and splenic hemosiderosis (persisting in recovery group animals) in both males and females at 8000 ppm. **No adverse effects.** NOEL (M)=126 mg/kg/day (2000 ppm) and (F)=131 mg/kg/day (2000 ppm) based on various treatment-related effects including decreased mean body weights, a decrease in mean hemoglobin (males only), an increase in mean white blood cells, an increase in mean creatinine, an increase in mean relative liver, spleen, and kidney weights, glycogen deposition in the hepatocytes, and splenic hemosiderosis. **Acceptable.** (Corlett, 3/18/99)

045; 162692; "28-Day Range Finding Study In Rats (Administration in Food)" (Bachmann, M., Ciba-Geigy Limited, Short/Long-Term Toxicology, Stein, Switzerland, Test No. 923060, 11/3/92). CGA-245704 tech. (Batch No. KGL 4208, purity=90.9%) was admixed to the feed at concentrations of 0 (feed), 500, 4000, or 12000 ppm (0, 45.9, 403, and 1070 mg/kg/day, respectively, for males, and 0, 44.8, 376, and 1000 mg/kg/day, respectively, for females) and fed to 5 Tif: RAlf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level for 4 weeks. No animals died. A treatment-related decrease in body temperature at Week 4 in both males and females was observed at 4000 and 12000 ppm. A treatment-related decrease in mean body weight in both males and females at 12000 ppm was observed. Treatment-related decreases in mean hemoglobin and hematocrit levels in males at 12000 ppm and in females at 4000 and 12000 ppm and in mean red blood cell levels in females at 4000 and 12000 ppm were observed. Treatment-related increases in reticulocytes and mean relative spleen weights were observed in both males and females at 12000 ppm. Macroscopic examination revealed enlarged spleens in both males and females at 12000 ppm. **No adverse effects.** NOEL (M)=403 mg/kg/day (4000 ppm) and NOEL (F)=44.8 mg/kg/day (500 ppm) (based on hematological parameters). **Supplemental study** (since the animals were treated for only 4 weeks, only 5 animals per sex per dose level were used, and no ophthalmological examinations were performed). (Corlett, 3/9/99)

047; 162699; "28 Day Oral Cumulative Toxicity Study in Rats (Gavage)" (Fankhauser, H., Ciba-Geigy Limited, Short/Long-Term Toxicology, Stein, Switzerland, Test No. 923137, 12/9/93). CGA-245704 tech. (Batch No. P.303011, purity=97.9%), suspended in 0.5% carboxymethylcellulose and 0.1% Tween 80 in distilled water, was administered by gavage once daily at concentrations of 0 (vehicle only), 10, 100, or 800 mg/kg/day to 10 Tif: RAlf (SPF), hybrids of RII/1 x RII/2 (Sprague-Dawley derived) rats per sex per dose level for 28 days. No animals died. No treatment-related clinical signs were observed. Treatment-related decreases in mean body weight, red blood cell, hemoglobin and hematocrit levels in females at 800 mg/kg/day were observed. A treatment-related increase in mean total bilirubin, and treatment-related decreases in mean protein and globulin levels in both males and females at 800 mg/kg/day were observed. Treatment-related increases in mean relative liver and spleen weights in both males and females at 800 mg/kg/day were observed. Microscopic examination revealed a treatment-related decrease in extramedullary hematopoiesis in the spleen, treatment-related necrosis of hepatocytes, and a treatment-related decrease in fatty atrophy in the bone marrow in females at 800 mg/kg/day. **No adverse effects.** NOEL (M/F)=100 mg/kg/day [based on decreased body weights (females), hematological parameters (females), clinical chemistry parameters (males and females), mean relative organ weights (males and females), and microscopic findings (females)]. **Supplemental study** (since the animals were treated for only 28 days). (Corlett, 3/15/99)

050; 162703; "3-Month Subchronic Oral Toxicity Study in Beagle Dogs" (Altmann, B., Ciba-Geigy Limited, Short-/Long-term Toxicology, Stein, Switzerland, Test No. 923138, 11/8/94). 821. CGA 245704 tech. (Batch No. P.303011, purity=97.9%) was administered orally in gelatin capsules once per day 7 days per week at concentrations of 0 (empty capsule), 10, 50, or 200 mg/kg to 4 beagle dogs per sex per dose level for 3 months [with 2 additional dogs per sex per

dose level at the 0 and 200 mg/kg/day levels to test recovery (4 week recovery period used)]. No animals died. No treatment-related clinical signs were observed. A treatment-related decrease in mean red blood cell count, hematocrit, and hemoglobin levels in both males and females at 200 mg/kg/day was observed during treatment (recovery group animals indicate reversibility of these effects). Treatment-related increases cholesterol, triglycerides, and phospholipids levels were observed in both males and females at 200 mg/kg/day during treatment (recovery group animals indicate reversibility of these effects). Treatment-related increases in mean relative liver weights in both males and females at 50 and 200 mg/kg/day at Week 14 were observed (recovery group animals indicated reversibility in males but not females). Microscopic examination revealed treatment-related pigmentation in liver Kupffer cells (persisting in some recovery group animals) in both males and females, and congestion (in males and females) and hemosiderosis (in males only) of the spleen at 200 mg/kg/day (recovery group animals indicate reversibility). **No adverse effects.** NOEL (M/F)=10 mg/kg/day based on increased mean relative liver weights. **Acceptable.** (Corlett, 3/31/99)

049; 162702; "28-Day Range Finding Toxicity Study In Beagle Dogs" (Altmann, B., Ciba-Geigy Limited, Short-/Long-Term Toxicology, Stein, Switzerland, Test No. 923130, 1/20/94). CGA-245704 tech. (Batch No. P. 303011, purity=97.9%) was administered orally in gelatin capsules daily 7 days per week at concentrations of 0 (empty capsule), 50, 250, or 500 mg/kg to 2 beagle dogs per sex per dose level for 28 days. No animals died. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight in males at 250 and 500 mg/kg and in females at 500 mg/kg at Weeks 3 and 4 was observed. A treatment-related decrease in mean food consumption in both males and females at 250 and 500 mg/kg at Weeks 3 and 4 was observed. Treatment-related decreases in mean red blood cell, hemoglobin and hematocrit levels in males at 500 mg/kg and in females at 250 and 500 mg/kg were observed. A treatment-related increase in mean cholesterol levels in both males and females at 250 and 500 mg/kg was observed. Treatment-related increases in mean relative liver and spleen weights at 250 and 500 mg/kg and in mean relative increases in kidney and adrenal weights at 500 mg/kg were observed in both males and females. Microscopic examination revealed treatment-related several treatment-related effects including splenic extramedullary hematopoiesis, splenic hemosiderosis, Kupffer cell hemosiderosis, and atrophy of cortex of thymus in both males and females at 250 and 500 mg/kg. **No adverse effects.** NOEL (M/F)=50 mg/kg [based on decreased body weights (males only) and food consumption, hematological parameters (females only), increased cholesterol levels, increased organ weights, and microscopic findings]. **Supplemental study** (since the animals were treated for only 28 days and only 2 animals per sex per dose level were used). (Corlett, 3/24/99)

046; 162698; "3-Month Range Finding Toxicity Study in Mice (Administration in Food)" (Fankhauser, H., Ciba-Geigy Limited, Short/Long-Term Toxicology, Stein, Switzerland, Test No. 923081, 9/3/93). CGA-245704 tech. (Batch No. KGL 4208, purity=90.9%) was admixed to the feed at concentrations of 0 (feed), 200, 1000, or 4000 ppm (0, 30.6, 152, and 624 mg/kg/day, respectively, for males, and 0, 47.4, 220, and 803 mg/kg/day, respectively, for females) and fed to 10 Tif: MAGf (SPF), hybrids of NIH x MAG mice per sex per dose level for 3 months. No animals died. No treatment-related clinical signs were observed. Treatment-related decreases in mean red blood cell, hemoglobin and hematocrit levels in females at 4000 ppm and a treatment-related increase in thrombocyte levels in both males and females at 4000 ppm were observed. A treatment-related increase in mean relative spleen weights in males beginning at 1000 ppm and in females beginning at 200 ppm was observed. Microscopic examination revealed treatment-related extramedullary hematopoiesis in the spleen in males beginning at 1000 ppm and in females beginning at 200 ppm, and treatment-related splenic hemosiderosis in both males and females beginning at 1000 ppm. **No adverse effects.** NOEL (M)=30.6 mg/kg/day (200 ppm) and NOEL (F)< 47.4 mg/kg/day (200 ppm) (based on increased mean relative spleen weights and extramedullary hematopoiesis in the spleen). **Supplemental study** (since no assays of blood biochemical parameters and no ophthalmological examinations were performed). (Corlett, 3/11/99)

(Dermal)

051; 162704; "28-Day Repeated Dose Dermal Toxicity Study In the Rat" (Hagemann, Ch., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Test No. 923135, 3/15/94). 822. CGA 245704 tech. (Batch No. P.303011, purity=97.9%), suspended in 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80, was applied to the clipped skin of 5 Tif: RAIf (SPF) hybrids of RII/1 x RII/2 rats per sex per dose at concentrations of 0, 10, 100, or 1000 mg/kg/day for 6 hours per day 5 days per week for 4 weeks using an occlusive dressing. No animals died. No treatment-related clinical signs were observed. Laboratory investigations (hematology and blood chemistry) revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related findings. **No adverse effects.** NOEL (M/F, systemic and dermal)=1000 mg/kg based on no treatment-related effects at HDT. **Acceptable.** (Corlett, 4/6/99)